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Clinical Infertility in Women

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Fertility results from coordinate functioning of components of the hypothalamic-pituitary-ovarian-genital axis. In normal women, ovarian sex steroid hormones act as the mediators of these interactions.

Infertility is a clinical manifestation of the failure of one or more of the components to function appropriately. Determining the locus of dysfunction provides the basis for rational treatment. For these purposes, both direct measurement of serum hormone levels and assessments of target organ function are utilized.

Introduction

The hormonal and gametogenic functions of the ovary, described earlier, are integrated into a system to assure fertility. When the system functions normally, oocytes escape from the ovary by ovulation and enter the fallopian tube where they undergo transformation into fertilizable ova. Then the pronuclei of sperm and ovum fuse (fertilization), and cell divisions produce a blastula. The blastula is transported into the uterus, where it implants if the endometrium is properly prepared and pregnancy ensues.

If the sequence of events described is to occur, function of the ovaries, the hypothalamic-pituitary unit, and the genital tract must be coordinated. Failure of appropriate functioning of these components results in infertility. In discussing clinical problems of infertility in women, we will examine first the coordination of these component interactions in normal women and then consider methods for evaluating the locus of disordered function in women who have been unable to conceive.

The Normal Hypothalamic-Pituitary-Ovarian-Genital Axis

The hypothalamus secretes hypophysiotropic hormones which stimulate the pituitary to produce the gonadotrophins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which can be measured in specimens of peripheral blood. Gonadotrophins are delivered to the ovaries where these hormones stimulate both follicular growth and steroid hormone synthesis and secretion. Although several sex steroid hormones are secreted, the important ones for our discussion consist in estradiol-17β (E_2), 17-α hydroxyprogesterone (17 OH-P), and progesterone (P). Concentrations of E_2, 17 OH-P, and P in peripheral blood are resultants of secretion by the ovaries and of metabolic processes, including metabolic clearance, that metabolize and remove these hormones from the blood (*1*). Comparisons of concentrations of these steroids in venous effluent from the two ovaries reveal that levels in peripheral blood in the second half of the preovulatory phase of the cycle reflect the secretory activity of the ovary containing the follicle which will give rise to the oocyte that is ovulated during that cycle (*2, 3*). Similarly, the concentrations of E_2, 17 OH-P, and P in venous effluent from the ovary containing the corpus luteum are much higher than those in the venous effluent from the contralateral ovary (*2, 3*). Thus, concentrations of E_2, 17 OH-P, and P in peripheral blood reflect the growth and maturation of the dominant follicle prior to and of the functioning corpus luteum after ovulation. Since the corpus luteum is derived from the follicle which ovulated, it is not surprising that there is evidence to support the contention that the functional capacity of the corpus luteum is predetermined by the hormonal milieu in which the preovulatory follicle develops (*4, 5*).

There is direct evidence in animal model systems (*6, 7*) and indirect evidence in the human (*8*) that within the ovary, the sex steroid hormones modulate growth and atresia of the ovarian follicles. In

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addition to modulating follicular growth and atresia within the ovary, the steroid hormones "feed back" on the hypothalamic-pituitary unit to modulate gonadotrophin synthesis and secretion (*9*). Thus levels of E_2, 17 OH-P, and P in peripheral blood are representative of the concentrations which perfuse the hypothalamic-pituitary unit to modulate gonadotrophin secretion and coordinate interactions of the two components during ovulatory cycles.

Steroid hormones also coordinate the functioning of the ovary and the hypothalamic-pituitary unit with that of the genital tract (*1*). These hormones stimulate proliferation of genital tract epithelia, regulate the quality and quantity of secretory products of these tissues, particularly the endometrium and the endocervical glands, and regulate the motility of the fallopian tubes and uterine contractions.

These component interactions are summarized diagramatically in Figure 1. From the figure, it is apparent that one could assess function of the components by measuring concentrations of sex steroid hormones and gonadotrophins in appropriately collected specimens of peripheral blood and determine the appropriateness of genital tract responses by monitoring changes in the morphology of the endometrium, in the quality and quantity of endocervical mucus, and in the character of vaginal epithelial cells. Since measurement of hormone concentrations in peripheral blood is expensive and time consuming, daily sampling is impractical. However, as we shall see, a limited number of samples, collected at appropriate times, provide critical diagnostic information.

Clinical Evaluation of Women with Infertility

In determining the pathophysiologic basis of infertility, it is important at the outset to establish that the husband produces adequate numbers of normal sperm. Failure to demonstrate that the quantity of semen is adequate and that the sperm are normally motile can result in unnecessary and expensive testing of perfectly normal women.

For purposes of this presentation, women who come to the physician for evaluation of the pathophysiologic basis of their failure to conceive may be grouped into three categories. The first consists of women who have undergone puberty but failed to conceive despite two years of unprotected intercourse. The second consists of women who have completed puberty normally but have subsequently ceased to menstruate, that is, women with secondary amenorrhea. The third group consists of women in whom menses failed to appear, that is women who have primary amenorrhea. Because diagnostic evaluation of these three groups of patients differs greatly this categorization makes a more rational approach to diagnosis possible.

In Women Who Menstruate

While primary and secondary amenorrhea constitute *prima facie* evidence of failure of coordinate function of the hypothalamic-pituitary-ovarian-genital axis, the converse is not true, since cyclic bleeding may occur despite either failure to ovulate or inadequate postovulatory corpus luteum function. For this reason, attention should be directed toward presumptive evidence for ovulation and corpus luteum function in women who have regular cyclic menses. Appropriately timed collections of one or two specimens of peripheral blood for measurement of progesterone concentrations with or without a simultaneous biopsy of the endometrium constitute an adequate test of the normality of corpus luteum function and thus of ovulation.

How can ovarian function be studied? Examining blood levels of sex steroid hormones collected at appropriate times in the cycle from women who are menstruating or at anytime from women with amenorrhea provide useful information. However, such measurements are expensive and may not be easily available to some physicians. As an alternative to measurement of blood hormone levels, it is possible to examine the sex steroid hormone target tissues in the genital tract for evidence of appropriate stimulation.

Examination of a specimen of endocervical mucus is a simple test for effects of estrogens and progestogens. Quality and quantity of endocervical mucus depend on the sex steroid hormones. The specimen can be obtained during vaginal examination and determinations made by gross inspection. Examination of endometrial morphology provides a second simple test of the prevailing sex steroid hormone milieu. Estrogens stimulate proliferation and progestogens stimulate secretory transformation of this epithelium, and sequential cyclic changes are characteristic.

Vaginal epithelial cells undergo characteristic changes in response to estrogens and progestogens secreted by the ovaries. These changes consist principally in variations in the extent of cornification and of shedding of these cells. If the patient has neither vaginal nor endocervical infection, some inferences can be drawn about the adequacy of ovarian estrogen secretion by microscopic examination of approximately stained smears of vaginal epithelial cells.

To facilitate timing of blood and target organ sampling, an indirect indicator of ovulation is the "thermogenic shift" in the basal body temperature curve (*10*). Graphs of daily basal body temperatures obtained consecutively between two episodes of vaginal bleeding show elevations of more than 0.5°C at or around the time of ovulation. This "shift" from lower to higher temperatures reflects activity of progestogens secreted by the ovulatory follicle on the thermoregulatory apparatus in the hypothalamus. While it constitutes a presumptive indicator of ovulation, the thermogenic shift is not an adequate measure of the adequacy of corpus luteum function, since levels of progesterone required to produce this effect are less than those required to produce an appropriate secretory transformation of the endometrium (*10*). Failure to observe the shift can be equated with failure of ovulation. To determine adequacy of corpus luteum function, specimens of blood obtained prior to and following the thermogenic shift will indicate whether serum progesterone levels have elevated appropriately after the thermogenic shift.

Assuming that direct and indirect evidence of ovulation and corpus luteum function have been found to be normal, one should question whether the genital tract secretions are conducive to proper traverse of the sperm through the endocervical canal, uterus and tubes to facilitate the encounter with the ovum. A postcoital test will determine whether this genital tract environment is "hostile" to the sperm; shortly after intercourse, vaginal secretions and endocervical secretions are examined for numbers and motility of sperm. For reasons not entirely clear presently, genital tract secretions of some women are spermatocidal and infertility ensues.

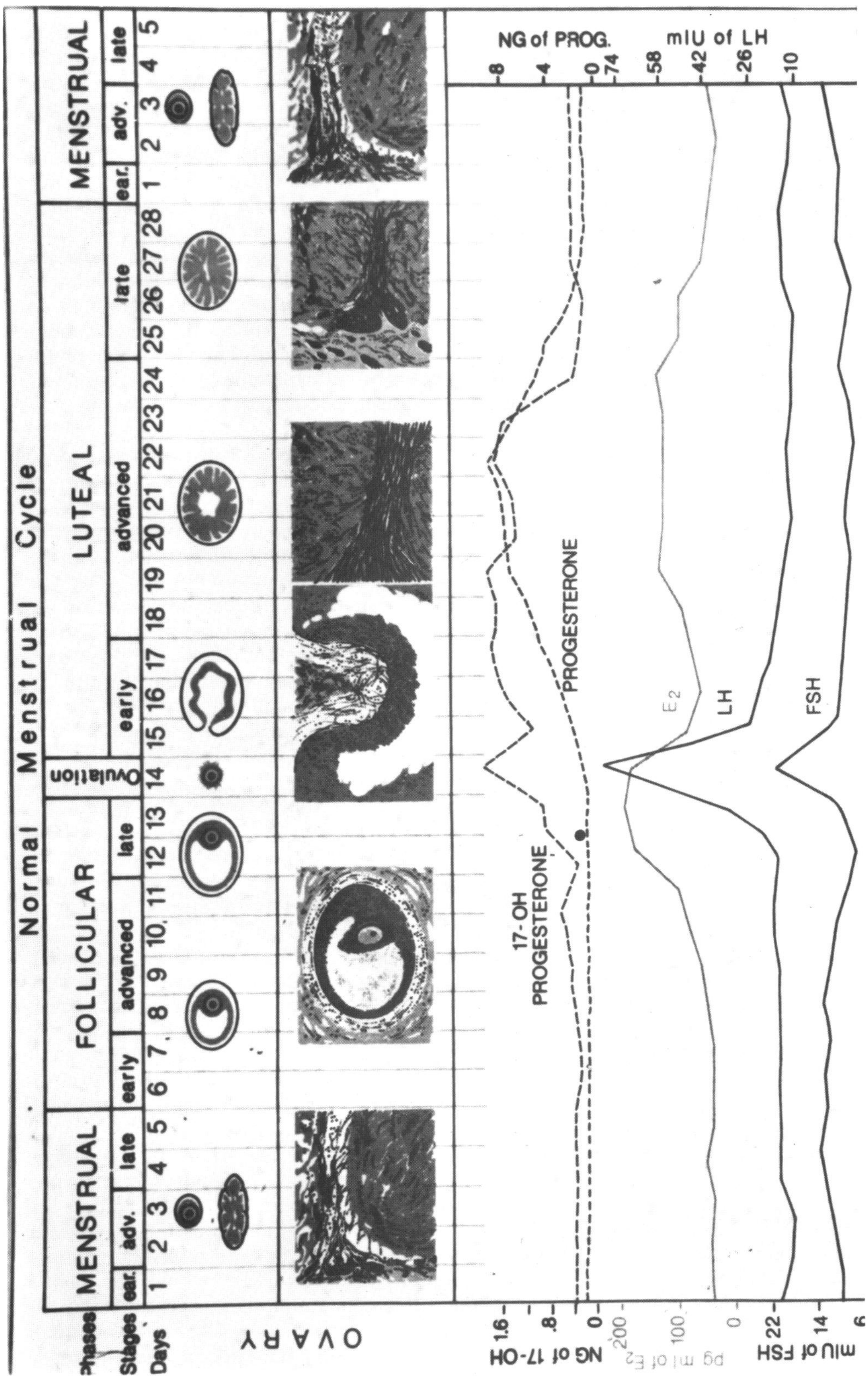
If adequate numbers of sperm with normal motility are present in the vagina and in the endocervical canal, one must raise the question as to whether there is some obstruction preventing the transfer of sperm into the fallopian tubes for the encounter with the ovum. Patency of the fallopian tubes is usually determined by the transcervical introduction of contrast media into the fallopian tubes followed by appropriate x-rays to ascertain if the contrast medium spills into the abdominal cavity.

In Women with Secondary Amenorrhea

Clinical evaluation of individuals who are not having cyclic menses, that is women with secondary amenorrhea, is somewhat more complex. In the overwhelming majority of instances, the abnormality will be found to be in either the hypothalamic-pituitary unit or the ovary. Measurement of the concentrations of sex steroid hormones and gonadotrophins in a single specimen of blood collected in the basal state provides diagnostically useful information in women in whom the cause of secondary amenorrhea is primarily due to depletion of oocytes from the ovary (*11*) or alternatively to refractoriness of the follicular apparatus to gonadotrophic stimulation (*12, 13*). In these women very high serum levels of follicle stimulating hormone and luteinizing hormone will be found comparable to those from post-menopausal women, reflecting low prevailing levels of E_2 and/or P. Atrophic vaginal epithelium and a significant reduction in the quantity of endocervical mucus reflect inadequate ovarian estrogen secretion. This evidence of low estrogen coupled with sustained high levels of FSH and LH in a basal specimen of blood is diagnostic of primary ovarian failure.

If ovarian failure has been ruled out, function of the hypothalamic-pituitary unit should be evaluated. For the purposes of this discussion abnormalities of the hypothalamic-pituitary unit which eventuate in secondary amenorrhea and infertility are classifiable into two major groups. The first consists of hypothalamic-pituitary dysfunction and the second consists of hypothalamic-pituitary failure. In persons with hypothalamic-pituitary dysfunction, hormone levels in the basal state are within the range of normal in virtually 100% of cases (*14, 15*). Moreover, changes in serum hormone concentrations in response to perturbations are likewise within normal limits. In general, administration of estrogens and progestogens will suppress pituitary gonadotrophin secretion and giving an antagonist to the biological effects of estrogen will enhance pituitary gonadotrophin secretion in these women (*10, 16*). In contrast to women with hypothalamic-pituitary dysfunction, women with hypothalamic-pituitary unit failure will have decreased concentrations of gonadotrophins in specimens of peripheral blood collected in the basal state and in the majority of instances, will fail to respond appropriately following perturbations (*14, 15*). Hence, in both groups measurement of hormone concentrations prior to and following perturbations will increase the diagnostic value of these determinations.

The simplest of the perturbation tests consists in the intramuscular or oral administration of a progestogen (*14, 15*). If the genital tract is patent, and the ovary has secreted sufficient estrogen to stimulate proliferation of the endometrium, the administration of a progestogen will be followed by vaginal bleeding within one week. If the person does not bleed, either the ovary has not secreted adequate amounts of estrogen or the endometrium is refractory.



Normal Menstrual Cycle
Phases
Stages
Days
MENSTRUAL
FOLLICULAR
Ovulation
LUTEAL
MENSTRUAL
ear.
adv.
late
early
advanced
late
early
advanced
late
ear.
adv.
late
OVARY
17-OH PROGESTERONE
PROGESTERONE
E2
LH
FSH
NG of PROG.
mIU of LH
NG of 17-OH
pg ml of E2
mIU of FSH

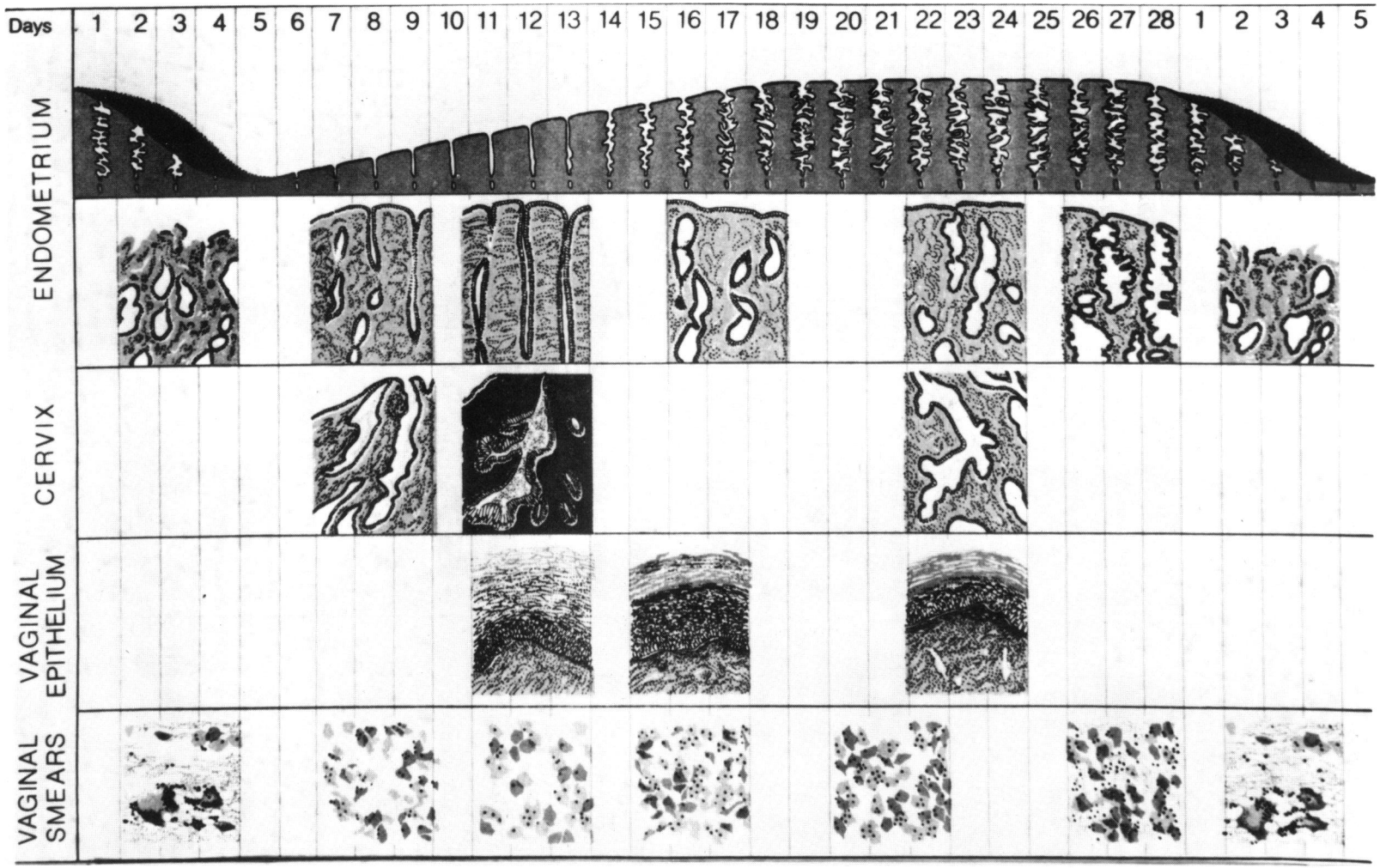


FIGURE 1. Coordinate changes in components of the hypothalamic-pituitary-ovarian-genital axis during the normal human menstrual cycle. Reproduced by permission from Ross and Vande Wiele (*1*).

To distinguish between these alternatives, it is necessary to give an estrogen for a period of 21 days to stimulate endometrial proliferation followed by the administration of the progestogen to induce bleeding. Failure to bleed after sequential estrogen and progestogen indicates refractory endometrium which cannot respond to normal quantities of sex steroid hormones (*17*).

If the individual fails to bleed in response to the progestogen alone, but bleeds following the administration of estrogen and progestogen, the pathophysiologic basis for the disorder may be in the ovary or in the hypothalamic-pituitary unit. On the other hand as noted above, if gonadotrophin levels are elevated, an ovarian disorder is probable. If levels of FSH and LH in the basal state are low in an individual who does not bleed following the administration of the progestogen, failure of the hypothalamic-pituitary unit is indicated, since normally the hypothalamic-pituitary unit should respond to low prevailing levels of estrogen with secretion of both FSH and LH (*15*). Once the diagnosis of hypothalamic-pituitary unit failure has been established, it is mandatory to determine the basis for the failure. In many instances, this can be discovered by radiographic examination of the sella turcica and appropriate other tests of anterior pituitary function.

In Women with Primary Amenorrhea

The diagnosis of infertility associated with primary amenorrhea usually requires more sophisticated testing. In addition to the measurements of hormones in the basal state and following perturbations, it is essential to rule out congenital malformations of the genital tract, sex chromosomal abnormalities, and genetic defects in adrenal or ovarian steroid hormone metabolizing enzyme systems which predispose to primary amenorrhea (*1*).

Treatment of Infertility

The extent to which exposure to noxious chemical agents in the environment predispose to the development of infertility in women remains to be determined. However, use of drugs such as oral contraceptives (*18*) or tranquilizers (*19*) may result in secondary amenorrhea. Stopping the drug will result in resumption of menses in some of these women.

Once the etiologic basis of infertility has been established, rational therapy is fortunately available for some of these women. In women with secondary amenorrhea who respond to a progestogen with vaginal bleeding, the administration of an estrogen antagonist is frequently sufficient to stimulate ovulation, permitting conception and successful pregnancy (*20*). Doses of these substances need to be titrated and administered under close surveillance of a physician in order to avoid the hyperstimulation syndrome which eventuates in multiple births. In women in whom failure of the hypothalamic-pituitary unit is the etiologic basis of infertility, administration of gonadotrophins extracted from the urine of postmenopausal women to stimulate follicular growth, followed by administration of HCG to stimulate ovulation will result in ovulation and successful pregnancy in about 30% of cases (*21*). Treatment of infertility in women with normal cyclic menses and adequate corpus luteum function is more complicated but is likewise successful in about 30% of cases.

In women with failure of the hypothalamic-pituitary unit secondary to pituitary tumors secreting prolactin, analogues of ergot which function as dopamine antagonists have been used successfully to reestablish cyclic ovulation followed by normal pregnancies (*22, 23*). In some of these women resection of the pituitary tumor results in resumption of normal functioning of the remaining normal pituitary tissue, cyclic menses, ovulation, and fertility (*24*).

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